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Case report

Incidental reduction in the size of liver hemangioma following use of VEGF inhibitor bevacizumab☆

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***Background/Aims*: Hepatic cavernous hemangioma is the second most common liver tumor after metastases. Vascular endothelial growth factor (VEGF) is recognized as an essential regulator of blood vessel growth. High VEGF expression leads to increased angiogenic activity in cavernous hemangioma endothelial cells. The use of specific antibodies directed against VEGF abolishes this vascular endothelial growth-promoting activity *in vitro*. Bevacizumab is a recombinant humanized monoclonal antibody directed against VEGF which is used for the treatment of metastatic colorectal cancer in combination with 5-fluorouracil-based regimens.**

***Methods*: We report a patient with invasive colorectal adenocarcinoma and suspected liver metastasis on radiological examination, who showed a significant decrease in the size of his liver lesions after bevacizumab treatment. Histology of the liver lesions revealed hemangioma with a strong staining for VEGF and anti-VEGFr2 antibody in the hemangioma endothelial cells. To date, surgical resection provides the only consistently effective method for treatment of hepatic hemangioma.**

***Conclusions*: This is the first documented case of hepatic hemangioma responsive to antiangiogenic therapy, suggesting a possible use for these agents in treating symptomatic patients without surgery. VEGF-signaling blockade including bevacizumab use poses a potential new treatment modality for vascular neoplasms in the liver and other sites.**

***Keywords*: Bevacizumab; Vascular endothelial growth factor (VEGF); Hemangioma; Angiogenesis**

1. Introduction

Hepatic cavernous hemangioma accounts for 73% of all benign liver tumors [1] and is the second most common tumor seen in the liver after metastases [2]. Vascular endothelial growth factor (VEGF) is recognized as an essential regulator of normal and abnormal blood vessel growth [3]. It is postulated that higher expression of VEGF and angiopoietins leads to increased angiogenic activity in cavernous hemangioma endothelial cells (CHECs) [1]. The use of specific antibodies directed against VEGF abolishes the vascular endothelial growth-promoting activity *in vitro* [4]. Bevacizumab is a recombinant humanized monoclonal antibody (93% human and 7% murine) directed against VEGF which is used for the treatment of metastatic colorectal cancer in combination with 5-fluorouracil (5-FU)-based regimen [3].

We report a patient with colorectal carcinoma and suspected liver metastasis on radiological examination who showed a significant decrease in the size of his liver

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lesions after being treated with bevacizumab post colectomy. Histological examination of the liver lesions revealed hemangioma; no metastatic colonic adenocarcinoma was identified. This is the first documented case of hepatic hemangioma responsive to antiangiogenic therapy, suggesting a possible use for these agents in treating symptomatic patients without surgery.

2. Case report

A 51-year-old male patient presented to the outpatient surgery department with a bloody bowel movement. He had undergone colonoscopy at another institution which revealed a tubulovillous adenoma in the right colon and a near obstructing lesion in the sigmoid colon. Repeat colonoscopy confirmed a large ulcerating mass in the sigmoid colon, but the right colonic lesion could not be visualized as the scope was unable to pass through the sigmoid colon mass. Biopsy of the sigmoid mass revealed invasive moderately differentiated adenocarcinoma. A staging multiphasic helical CT scan was performed, revealing a 3.6 × 2.8 cm lesion in segment VI of the liver (Fig. 1), suspicious for metastasis. The enhancement characteristics of this lesion were not consistent with hemangioma. There was also an 8 mm hypodense lesion in segment V and a similar 8 mm lesion at the junction of segments II and IVa. The family history was significant for the mother being diagnosed with colon cancer at 74 years of age.

A staged approach for the management of the patient was planned, including colectomy followed by chemotherapy and subsequent liver resection after reassessment of the liver tumors. The patient underwent right hemicolectomy with ileocolic anastomosis, sigmoid colectomy with colorectal anastomosis and loop ileostomy. The right colonic lesion was diagnosed as a villous adenoma. The sigmoid colon mass was a moderately differentiated invasive adenocarcinoma (Fig. 2). Twenty-nine lymph nodes were isolated and were negative for tumor metastasis. The primary tumor was staged as pT1N0M1. The patient then received four rounds of FOLFOX chemotherapy (a regimen of oxaliplatin, 5-fluorouracil and leucovorin) and bevacizumab. Repeat CT scan showed an interval decrease in size of the right posterior hepatic lesion. The previously noted lesion was smaller and less well defined than the prior study. Its borders were not well defined; however, it was estimated at approximately 2.5 × 2.5 cm (Fig. 3). Other previously seen lesions were not identified.

At the time of the hepatic resection, the patient underwent an intraoperative ultrasound which revealed a single lesion approximately 2–3 cm in diameter in segment VI of the liver along with an additional smaller

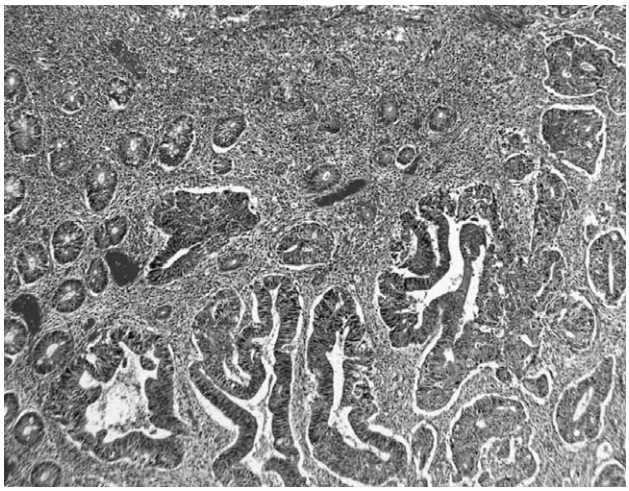

Fig. 2. Histology of the sigmoid colon mass reveals a moderately differentiated invasive adenocarcinoma. (H&E 20×).

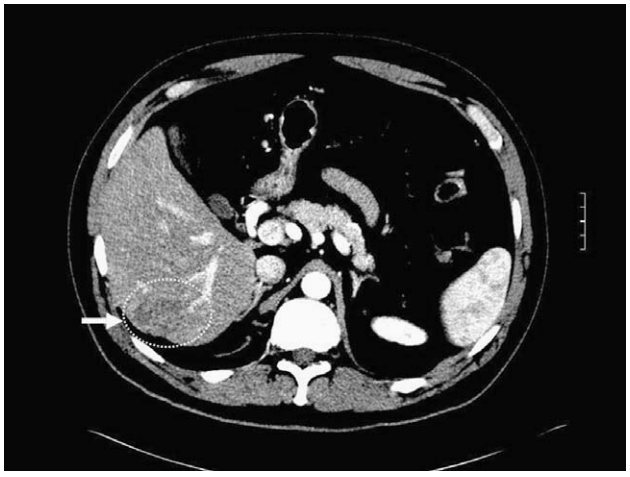

Fig. 1. CT Scan showing pre-treatment dominant lesion (3.6 × 2.8 cm) within segment VI of the liver, suspicious for metastasis (dotted line and arrow).

Fig. 3. Post-bevacizumab CT scan showing a reduction in the size of the dominant lesion with blurring of borders (dotted line and arrow).

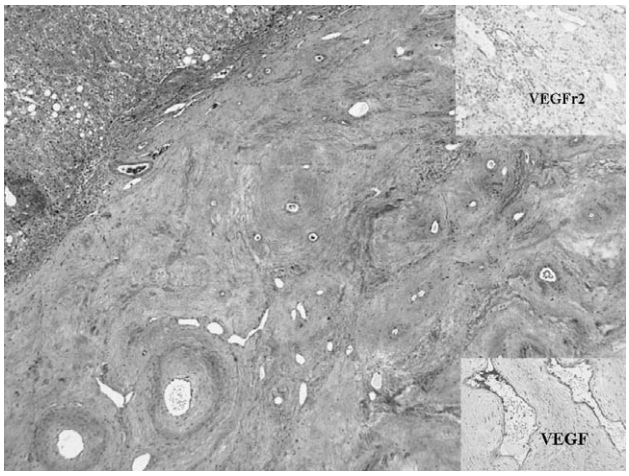

Fig. 4. Histology of the liver lesions reveal hemangioma with strong and diffuse staining for VEGF (inset) and VEGFr2 (H&E 20×, H&E 40×).

lesion in segment IV. A partial resection of hepatic segments VI and IV was performed. Microscopic examination of both lesions revealed benign cavernous hemangioma. Both lesions showed prominent fibrous stroma as well as benign and variably dilated vascular spaces (Fig. 4). Cytologic atypia was not identified. Metastatic adenocarcinoma was not identified. Immunohistochemical staining for VEGF (Chemicon International, Inc., Temecula, CA) revealed strong, diffuse staining in the hepatic hemangioma endothelial cells, while the liver sinusoidal endothelial cells were negative (Fig. 4 inset). Immunostaining for anti-VEGFr2 (Cell Signaling, Inc., Danvers, MA) also revealed a strong, diffuse staining in the hepatic hemangioma endothelial cells while the liver sinusoidal endothelial cells also showed some positivity (Fig. 4, inset).

3. Discussion

Hepatic hemangioma is the commonest benign tumor in the liver, with a frequency of up to 7.3% and varying in size from a few millimeters to nearly replacing the liver in diffuse haemangiomatosis [5,6]. Hepatic hemangiomas are usually asymptomatic, incidental lesions [1]. Common symptoms in infancy include hepatomegaly and congestive heart failure [7]. In adults, hepatic hemangiomas may be associated with right upper quadrant pain or discomfort, nonspecific symptoms, or jaundice [6]. Although rare, the most severe presentation is a ruptured hemangioma with hemorrhagic shock [1].

The pathogenesis of cavernous hemangioma remains unclear, but two hypotheses have been proposed. One proposes that these tumors result from abnormal angiogenesis, with an increase of pro-angiogenic factors like VEGF and matrix metalloproteinases (MMP) and downregulation of angiogenesis inhibitors [8,9]. Others suggest genetic defects may be involved [10].

In the early 1970s, Folkman et al. [11] identified a tumor-angiogenesis factor that was mitogenic to tumor capillary endothelial cells and suggested that blocking this factor might arrest tumor growth. VEGF is now recognized as an essential regulator of normal and abnormal blood vessel growth [3]. VEGFs are encoded by a family of genes including VEGF-A, -B, -C, -D, and placental growth factor (PGF) [12]. VEGF- A, -B, and PGF are predominantly required for blood vessel formation, while VEGF-C and -D are essential for the formation of lymphatic vessels [3]. The biological functions of VEGF are mediated through binding to VEGFR-1 (Flt-1), VEGFR-2 (KDR/Flk-1), and VEGFR-3 (Flt-4) receptors [13]. VEGFR-2 is the predominant receptor in angiogenic signaling and acts via the PI 3-kinase/Akt pathway and the classical Ras-dependent signaling cascade impinging on MAP kinases such as ERK1 and ERK2 [3]. Zhang et al. found that the expression of VEGF-A was increased in all kinds of hepatic CHECs when compared to human liver sinusoidal endothelial cells (LSECs), indicating that the increased angiogenic activity in CHECs might be related to a higher expression of VEGF [1].

Stromal cells cultured from surgically removed life-threatening hemangiomas released an endothelial cell mitogen *in vitro* that was indistinguishable from VEGF, and systemic injections of neutralizing anti-VEGF antibodies inhibited the angiogenic response in nude mice grafted with neonatal hemangioma cells [4] VEGF blockade in tumors has been shown to have a direct and rapid antivascular effect through deprivation of tumor vascular supply and inhibition of endothelial proliferation [3]. Isner et al. observed that transduction of a plasmid coding for VEGF in human ischemic arteries led to the formation of cutaneous hemangioma that regressed when VEGF bioavailability decreased, confirming the pathophysiological role of VEGF in this disease [14].

To date, whenever treatment for hepatic hemangioma is indicated, surgical resection provides the only consistently effective method reported but may not be feasible in patients with in patients with multiple hemangiomas, extensive hilar involvement or multiple comorbidities [15]. Embolization, hepatic artery ligation, radiation therapy and corticosteroids have been tried in these patients but have limited success and are often associated with significant morbidity [6]. Drugs that interfere with VEGF signaling might open up a new field in hemangioma treatment. Bevacizumab is a recombinant humanized monoclonal antibody directed against VEGF and approved for treatment of metastatic colorectal cancer in combination with a 5-fluorouracil-based regimen. Studies of bevacizumab alone or in combination with chemotherapy reported encouraging efficacy and safety results in hepatocellular, ovarian, renal cell,

and pancreatic cancers, as well as in melanoma and soft tissue sarcoma [3].

Mitchell et al. [16] reported bevacizumab to induce a strong biological and clinical response in a patient of symptomatic hereditary hemorrhagic telangiectasia with liver involvement complicated by high-output cardiac failure, portal hypertension and cholestasis. There was a marked diminution of hepatic vascularity, a twofold reduction in liver volume and normalization of cardiac output, thus alleviating the need for a liver transplantation. Therapy was well tolerated. The authors suggested that biological agents targeting angiogenic growth factors represent a novel form of therapy for these patients [16]. A combination of intravitreal bevacizumab with photodynamic therapy has been reported to successfully treat a case of juxtapapillary retinal capillary hemangioma (RCH) [17]. Intravitreal bevacizumab has also been shown to be therapeutic in patients with vasoproliferative retinal tumor [18] and show partial therapeutic response when used systematically to treat juxtapapillary RCH [19]. However, further studies are yet needed to assess the efficacy of bevacizumab in vasoproliferative tumors.

In our case, the incidental use of bevacizumab led to a decrease in the size of the dominant lesion and completely treated the other smaller lesions visualized on the initial CT scan. The fact that these lesions were actually hemangiomas and that VEGF plays a central role in pathogenesis of hemangioma suggests that bevacizumab (an anti-VEGF antibody) caused regression of hemangioma in our patient. We believe that this serendipitous concurrence holds promise in the use of bevacizumab for treatment of not only hepatic hemangiomas but hemangiomas in other parts of the body as well.

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